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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

STOICA, ELLY GERALD

ART UNIT

PAPER NUMBER

1647

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/522,826	Applicant(s) MENART ET AL.	
	Examiner ELLY-GERALD STOICA	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 February 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,5-7,10,12-17,19-21,23-26 and 38-55 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 5-7, 10, 12-17, 19-21, 23-26 and 38-55 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/22/2010 has been entered. Claims 1, 5-7, 10, 12-17, 19-21, 23-26, 38-42 and the newly added claims 43-55 are pending and are currently examined.

Withdrawn claim rejections

2. The rejection of claims 1, 4-7, 10, 12-17, 19-21, 23-26, 38-39 and 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

3. The rejection of claims 1, 4-7, 10, 12-17, 19-20, 23-26, and 38-42 under 35 U.S.C. 103(a) as being unpatentable over Patra et al. (Protein Expression and Purification 18,182-192, 2000) in view of Panda et al. (J. Biotechnology, 75, 161-172, 1999) and in further view of Souza LM (U.S. Pat. No. 4,810,643), Ambrosius et al. (U.S. Pat. No. 5,618,927), Camble et al. (U. S. Pat. 5,773,581), and Pelleymounter et al. (U.S. Pub. 20020009798) is withdrawn in view of the amendments to the claims and persuasive arguments of Applicant.

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4. The rejection of claim 21 under 35 U.S.C. 103(a) as being unpatentable over Patra et al. (Protein Expression and Purification 18,182–192, 2000) in view of Panda et al. (J. Biotechnology, 75, 161-172,1999) and in further view of Souza LM (U.S. Pat. No. 4,810,643), Ambrosius et al. (U.S. Pat. No. 5,618,927), Camble et al. (U. S. Pat. 5,773,581), Pelleymounter et al. (U.S. Pub. 20020009798) and Donnelly et al. (U.S. Pat. No. 6,677,139) is withdrawn in view of the amendments to the claims and persuasive arguments of Applicant.

New claim rejections

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 5-7, 10, 12-17, 19-21, 23-26, 38-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific conditions (E.coli BL21/DE3 pET3a/P-Fotp5, which is an inducible bacterial system and is grown at 25°C; the washing of inclusion bodies is performed with water or Tris/HCl at a pH8.0), does not reasonably provide enablement for the full breadth of the independent claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

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The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The independent claim¹ is drawn to a process for the production of a biologically active G-CSF, comprising:

- expressing G-CSF as a heterologous protein in an expression system comprising a cultivated organism, wherein the protein is expressed as a substantially correctly folded protein precursor in non-classical inclusion bodies;
- regulating one or more cultivation parameters selected from the group consisting of temperature of cultivation, composition of cultivation medium, induction mode, principle of performing the fermentation, addition of a stress induction agent, and co-expression of auxiliary proteins, wherein regulating the one or more parameters increases the proportion of substantially correctly folded protein precursor present in the inclusion bodies in the cells, relative to the proportion of substantially correctly folded protein precursor present in inclusion bodies in cells of an organism not cultivated by regulating said parameters;
- isolating the inclusion bodies from the cells of the organism;
- optionally, washing the inclusion bodies;

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solubilizing the substantially correctly folded protein precursor from the inclusion bodies under non-denaturing conditions by contacting the non-classical inclusion bodies with a non-denaturing aqueous solvent having a pH of about 8.0; and purifying the biologically active protein from the solubilized substantially correctly folded protein precursor wherein the process for the production of the active protein is free from any denaturation and renaturation of the protein.

The process of production may be performed in yeast or bacteria and the proportion of the heterologous protein to the total protein mass of the cell is at least higher than 10% and as high as 30%. The temperature of cultivation ranges from 20°C to 30°C. The inducer may be IPTG or lactose or NaCl and present in a concentration from 0.1mM to 1 mM. The inducer is added at the beginning of the fermentation, which may be in a batch mode, fed batch mode in one or more flasks. The limitations that the claims 19-20, 23-26, 38 and 39 add consist of specific fermentation media (GYST, GYSP, LYSP LYST, LBON or GYSPON) and the use of non-denaturing solution of N-Lauroyl sarcosine in ranges of about 0.1% to about 0.25% mass per volume and a high solubilizing concentration of a buffer which may be HEPES. Further limitation is claimed as a minimal specific activity of G-CSF of 10^7 IU/mg.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and

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8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The prior art is aware of certain growing conditions which lead to inclusion bodies that are capable of being solubilized without being exposed to denaturing agents (i.e., inclusion bodies containing correctly folded proteins) for specific polypeptides (Gonzales-Villasenor, L.I., U.S. Pub. 20030166062; Li et al. U.S. Pat. 5,912,327; Patra et al., Protein Expression and Purification, 18, 182-192, 2000). However, the examples are targeted to specific proteins and also the art mentions that the process is still not considered routine and individual proteins have different conditions to be determined by trial and error experiments, especially for big proteins with multiple disulfide bonds in their correctly folded structure (Georgiou et al., Current Opinion in Biotechnology 7, 190-197, 1996- Introduction and Conclusion sections).

The specification presents detailed guidance and working examples for G-CSF only. In the working examples, only one type of bacteria is used: E.coli BL21/DE3 pET3a/P-Fotp5, which is an inducible bacterial system and is grown at 25°C. The washing of inclusion bodies is performed with water or Tris/HCl at a pH8.0. It is apparent that these are conditions *sine qua non* for obtaining the “non-traditional inclusion bodies” containing correctly folded G-CSF. However the breadth of the claims is directed to any bacterial system or yeast, without specifying the induction capability and at any temperature of growth. Applying the general directions as exemplified for G-CSF would not put the skilled artisan in possession of the invention since the process and the product cannot be judged as successful until experimentation is performed. The

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specification offers examples which all rely on the minimal conditions enumerated *supra* and even acknowledges that if the temperature conditions are not met or the buffers contain detergents, the formation of “non-classical inclusion bodies” cannot be obtained. As such, beyond the minimal conditions presented, the specification is just a hypothetical process that is uncertain in its feasibility and a huge amount of experimentation is needed to validate it for all the conditions possible.

Due to the large quantity of experimentation necessary to generate the vast number variants for the conditions in the claims; the lack of direction/guidance presented in the specification regarding the successful use of a different set of basic conditions; the absence of working examples directed to other basic conditions; the state of the prior art which establishes the unpredictability of obtaining correctly folded proteins in the inclusion bodies any other conditions; and the breadth of the claims which fail to present the minimal conditions necessary for the formation of the non-classical inclusion bodies, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 9:00-18:30 M-Th and 9:00-18:30 alternate F.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Elly-Gerald Stoica/
Examiner, Art Unit 1647